

### **REMARKS**

Applicant respectfully requests reconsideration. Claims 1-13, 16-21, 26, 28, 30, 34, 36, 38-41 and 44-48 were previously pending in this application. Claims 9, 11, 13, 17 to 21, 26, 28, 30, 34, 36, 38, 39, 41, and 44 to 48 are currently withdrawn.

Applicant thanks the Examiner for the helpful interview conducted on August 26, 2010 with Applicant's representatives. As discussed with the Examiner in that interview, claims 1 and 16 have been amended to recite that the claimed anti-Tumor Necrosis Factor-alpha (anti-TNF-alpha) polypeptide comprises at least two anti-TNF-alpha single domain antibodies. During the interview, unexpected results with such polypeptides were also discussed. Comments below reflect and expand upon that discussion. Claim 9 has been amended to include the correct dependency based on the amendment of claim 1 and cancellation of claim 8. Claims 6, 8, 11, 17-21, and 46-48 are canceled in this Amendment without prejudice or disclaimer. Applicant reserves the right to pursue the subject matter of the canceled claim in a related application.

### **Double Patenting Rejections**

1. The Examiner provisionally rejected claims 1-8, 10, 12, 16, 21, and 40 as allegedly being unpatentable over claims 1 to 6, 8, 44, 47, and 66 of copending Application No. 10/534,349.

The instant claims as amended are not obvious over the claims of the '349 application as amended. Accordingly, withdrawal of the rejection of claims 1-8, 10, 12, 16, 21, and 40 is respectfully requested.

2. The Examiner provisionally rejected claims 1-8, 10, 12, 16, 21, and 40 as allegedly being unpatentable over claims 1 to 15, 22, 25 to 39, and 46 of copending Application No. 11/788,832.

The Examiner is respectfully requested to defer further consideration of the double patenting rejection until an allowable set of claims have been obtained in this application. If the provisional nonstatutory obviousness-type double patenting rejection is the only rejection remaining in the earlier filed of the two pending applications, then the Examiner should withdraw the rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. MPEP 804 I.B.1.

3. The Examiner provisionally rejected claims 1-8, 10, 12, 16, 21, and 40 as allegedly being unpatentable over claims 10, 11, 22, 24, 25, 27, and 30-33 of copending Application No. 11/804,647.

The Examiner is respectfully requested to defer further consideration of the double patenting rejection until an allowable set of claims have been obtained in this application. If the provisional nonstatutory obviousness-type double patenting rejection is the only rejection remaining in the earlier filed of the two pending applications, then the Examiner should withdraw the rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. MPEP 804 I.B.1.

#### Rejections Under 35 U.S.C. § 103

1. The Examiner rejected claims 1, 16, 21 and 40 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rathjen et al. (WO 91/02078A1), in view of Els Conrath et al. (J. Biol Chem 2001). Applicant respectfully requests reconsideration of the rejection.

Applicant submits that the invention as now claimed is not obvious in view of the unexpected results demonstrated in the specification as filed for anti-Tumor Necrosis Factor-alpha (anti-TNF) polypeptides comprising at least two anti-TNF-alpha single domain antibodies.

Specifically, Applicant's specification provides data that shows the antagonistic efficacy of bivalent, trivalent and tetravalent anti-TNF polypeptides. For example, Example 4, beginning in the paragraph bridging pages 56 and 57, shows that a molecule with two TNF binding single domain antibodies (bivalent format) is 400-fold more effective (IC50 of 30 pM) than the monovalent TNF binder VHH#3E (IC50 of 12 nM) and even more effective than the chimeric antibody Remicade (IC50 of 50 pM). See, page 57, lines 1-11. See also Figure 3. As stated in the specification, molecules with three or four TNF binding single domain antibodies have even higher efficacy: "Increasing the avidity even more leads to a still better antagonistic behaviour: the trimeric VHH has an IC50 of 20 pM and the tetravalent format 6 pM. All higher avidity formats of the VHH are more efficient than Remicade . . . ." See, page 57, lines 11-15. Indeed, in one case, a 1000-fold increase in IC50 was observed with a bivalent form. Id. at lines 22-25.

When tested with VHH generated against mouse TNF, the "same unexpected effect of avidity on antagonistic behaviour was observed . . ." and "the unexpected improvement of the antagonistic characteristics" was again observed. Please see page 57, lines 17-25, and Figure 14.

Applicant further indicated the surprising and unexpected nature of these results in the specification at page 20, lines 11-21.

PCT published application WO2006/122786 (also published in the US as PG Pub 2010/0297111) provides additional data that shows significantly increased activity for bivalent anti-TNF-alpha single domain antibody constructs.<sup>1</sup> For example, Applicant submits that results in the following Examples, Tables and Figures sections of WO2006/122786 are consistent with the results

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<sup>1</sup> WO2006/122786 was published after the effective filing date of the present application.

shown in the instant application, as described above: Examples 10-13, 16, 21, 22, 33, 35-38, and 55-58; Figures 9-14 and 20; and Tables 12-14, 16, 20, 22, 23, 30, 32, and 45.

Therefore, Applicant has demonstrated unexpected results for the claimed polypeptides, which supports the nonobviousness of the claimed invention. Accordingly, withdrawal of this rejection is respectfully requested.

2. The Examiner rejected claim 1, 10, 16, 21 and 40 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rathjen et al. (WO 91/02078A1), in view of Casterman et al. (EP 584421 A1). Applicant respectfully requests reconsideration.

As described above, Applicant has demonstrated unexpected results for the claimed polypeptides. The Casterman et al. reference did not teach the unexpected effect of multivalency of the claimed polypeptides, and would not have provided to the skilled person any expectation that isolated anti-TNF-alpha polypeptides comprising at least two anti-TNF-alpha single domain antibodies would have such unexpectedly favorable properties. Thus the combination of the Rathjen et al. and Casterman et al. references would not have rendered the claimed invention obvious.

Accordingly, withdrawal of this rejection is respectfully requested.

3. The Examiner rejected claims 3, 4, 7, 8 and 12 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rathjen et al. (WO 91/02078A1), in view of Els Conrath et al. (J. Biol Chem 2001) as applied to claims 1, 16, 21 and 40 above, and further in view of Kontermann et al. (U.S. patent No. 6,759,518).

As described above, Applicant has demonstrated unexpected results for the claimed polypeptides. The Conrath et al. reference and Kontermann et al. reference did not teach the unexpected effect of multivalency of the claimed polypeptides, and would not have provided to the skilled person any expectation that isolated anti-TNF-alpha polypeptides comprising at least two anti-TNF-alpha single domain antibodies would have such unexpectedly favorable properties. Thus the combination of the Rathjen et al., Conrath et al. and Kontermann et al. references would not have rendered the claimed invention obvious.

Accordingly, withdrawal of this rejection is respectfully requested.

4. The Examiner rejected claims 3, 4, 7, 8 and 12 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rathjen et al. (WO 91/02078A1), in view of Casterman et al. (EP 584421) as applied to claims 1, 16, 21 and 40 above, and further in view of Kontermann et al. (U.S. patent No. 6,759,518).

As described above, Applicant has demonstrated unexpected results for the claimed polypeptides. The Casterman et al. reference and Kontermann et al. reference did not teach the unexpected effect of multivalency of the claimed polypeptides, and would not have provided to the skilled person any expectation that isolated anti-TNF-alpha polypeptides comprising at least two anti-TNF-alpha single domain antibodies would have such unexpectedly favorable properties. Thus the combination of the Rathjen et al., Casterman et al. and Kontermann et al. references would not have rendered the claimed invention obvious.

Accordingly, withdrawal of this rejection is respectfully requested.

**CONCLUSION**

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response that is not covered by an authorization to charge a credit card, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. A0848.70005US00.

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